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produced when FR-900506 is linked to an immunogenic carrier, such as BSA, to increase the immunogenicity of FR-900506. Further, the Examiner stated that FR-900506 is first converted to an ester of a dicarboxylic acid, such as succinic acid, then the ester is reacted with N-hydroxysuccinimide, resulting in an activated ester with BSA (see Example 1). The Examiner contended that FR-900506 has similar structural features and biological activity as rapamycin. Thus, the Examiner concluded that it would have been obvious for one skilled in the art to use rapamycin taught by Caufield et al, and conjugate the rapamycin to an immunogenic protein to increase the immunogenicity thereof, and to produce monoclonal antibodies using the methods taught by Niwa et al.

For the following reasons, Applicants respectfully traverse the Examiner's rejection as if applied to the claims of the present application.

As noted by the Examiner, Caufield et al does not teach or suggest monoclonal antibodies having binding specificity to a rapamycin.

Accordingly, Applicants respectfully submit that the present invention is not taught or suggested by Caufield et al, and for the following reasons, it is equally clear that Niwa et al does not provide the deficiencies that exist therein.

Even assuming arguendo that there is structural similarity between FR-900506 of Niwa et al and rapamycin, Applicants respectfully submit that even minor structural differences render unobvious the ability to obtain the claimed antibodies. Thus, the Examiner's rejection is nothing more than it would have been "obvious-to-try" to obtain the claimed antibodies using the

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process of Niwa et al as applied to a rapamycin of Caufield et al. However, "obvious-to-try" is an improper basis for issuing a rejection under 35 U.S.C. § 103. Rather, there must be a reasonable expectation of success for a proper obviousness rejection. Applicants respectfully submit that no such reasonable expectation of success exists because it was well-known in the art that even minor structural differences can effect the antigenicity of a particular molecule. For example, as shown in Adamczyk et al, *J. Immun. Methods*, 162:47-58 (1993); a copy of which is attached hereto, antisera against amitriptyline does not have significant cross-reactivity with nortriptyline and vis-a-versa, even though these compounds contain only a minor structural difference (see Figure 1 and Table I thereof). Similarly, Adamczyk et al, *J. Immun.*, 163:187-197 (1993), a copy of which is attached hereto, shows that antisera against desipramine does not have significant cross-reactivity with imipramine and vis-a-versa, even though these compounds contain only a minor structural difference (see Figure 1 and Table I thereof (also see Adamczyk et al, *Therapeutic Drug Monitoring*, 15:436-439 (1993); and Adamczyk et al, *Therapeutic Drug Monitoring*, 16:298-311 (1994), a copy of each of which is attached herewith).

Furthermore, Applicants respectfully submit that no such reasonable expectation of success exists in the present case because of *in vivo functional differences* between rapamycin and FR-900506, which were known as of the effective filing date of the present application.

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More specifically, at the time of the effective filing date of the present application, i.e., in 1993, it was known that FR-900506 blocks T-cell receptor (TCR)-induced T cell activation but does not directly affect B cell antibody production (Stevens et al, *Transpl.*, 51:1240-1244 (1991); and Morikawa et al, *Transpl.*, 54:1025-1030 (1992); a copy of each of which is attached hereto). In addition, it was known that FR-900506 actually augmented antibody production in some models (Yamamoto et al, *Immunol.*, 69:222-227 (1990); a copy of which is attached hereto). Thus, one would have expected that antibodies could be raised to FR-900506.^{1/}

On the other hand, it was known that rapamycin directly blocks antibody production from B cells, and also blocks T cell activation, and can inhibit T-dependent antibody production (Luo et al, *Transpl.*, 53:1071 (1992); a copy of which is attached hereto). Thus, one would have expected that there would be difficulty in raising antibodies to rapamycin because rapamycin inhibits antibody formation.

It was also known as of the effective filing date of the present application that both FR-900506 and rapamycin inhibit T cell proliferation via different mechanisms. That is, it was known that FR-900506 inhibits TCR-induced activation, but FR-900506 does not block proliferation of T cells stimulated by anti-CD28 antibodies or IL-2 (Dumont et al, *J. Immunol.*,

^{1/} While FR-900506 was known to inhibit T cell response in liver transplants, and to prolong graft survival, FR-900506 did not prevent the rise of IgM antibody in the graft (Langer et al, *Am. J. Pathol.*, 143:85-98 (July 1993); a copy of which is attached hereto).

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144:251-258 (1990); a copy of which is attached hereto). Further, FR-900506 blocks TCR-induced production of IL-2 and other cytokines (Tocci et al, *J. Immunol.*, 143:718-726 (1989); a copy of which is attached hereto).

On the other hand, rapamycin blocks proliferation of T cells stimulated by IL-2 and other cytokines (Dumont et al (1990), *supra*). One mechanism of such action is that rapamycin blocks the IL-2-induced, growth-dependent activation of and signaling by the 70kDa S6 protein kinase (pp70^{S6kinase}) (Chung et al, *Cell*, 69:1227-1236 (1992); a copy of which is attached hereto). In contrast, FR-900506 has no effect on T cell proliferation induced by IL-2 (Dumont et al (1990), *supra*), a copy of which is attached hereto); and does not block the IL-2-induced activation of pp70^{S6kinase} (Chung et al, *supra*).

Furthermore, during TCR-induced T cell activation, FR-900506 binds to FK506 Binding Protein (FKBP) and subsequently, the FR-900506/FKBP complex blocks the ability of the rapid intracellular accumulation of Ca⁺⁺ to activate the calmodulin-calcineurin complex, stimulating the phosphatase activity of calcineurin (O'Keefe et al, *Nature*, 357:692-694 (1992); Clipstone et al, *Nature*, 357:695-697 (1992); and Schreiber et al, *Immunology Today*, 13:136-142 (1992); a copy of each of which is attached hereto). In the absence of FR-900506, the activation of the calmodulin-calcineurin complex results in the dephosphorylation of the cytoplasmic subunit of NF-AT (nuclear factor of activated T cells), which then migrates to the nucleus and binds to the nuclear subunit of NF-AT. The NF-AT complex binds to its recognition sequence on the DNA, and

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is a major transcription factor stimulating the transcription of IL-2 and other cytokines.

In contrast, rapamycin does not affect the activation of calcineurin phosphatase activity (Liu et al, *Cell*, 66:807-815 (1991); a copy of which is attached hereto), and generally does not affect cytokine transcription (Dumont et al *J. Immunol.*, 144:1418-1424 (1991); and Bierer et al, *Proc. Natl. Acad. Sci. USA*, 87:9231-9235 (1990); a copy of which is attached hereto). In fact, rapamycin in high molar excess (50-100-fold) is a functional antagonist for FR-900506-inhibitory activity on early gene expression of activated T cells (Dumont et al (1991), *supra*; and Bierer et al, *supra*).

Hence, Applicants respectfully submit that, as of the effective filing date of the present application, i.e., in 1993, it was unpredictable that antibodies could be generated against rapamycin even though it was known that antibodies could be generated against FR-900506. This is because the mechanism of action of rapamycin and FR-900506 are very different, and rapamycin was known to inhibit antibody formation, whereas FR-900506 did not inhibit antibody formation, and in fact FR-900506 was shown to augment antibody production in some animal models. Thus, there was no reasonable expectation that one could successfully obtain antibodies to rapamycin based on the teachings of Niwa et al.

Accordingly, Applicants respectfully submit that the present invention is not taught or suggested in Caulfield et al alone, and that the combination thereof with the teachings of Niwa et al can only be made in hindsight, which is legally improper.

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The Examiner is invited to contact the undersigned at his Washington telephone number on any questions which might arise.


Respectfully submitted,

Gordon Kite
Registration No. 30,764

**SUGHRUE, MION, ZINN,
MACPEAK & SEAS, PLLC**
2100 Pennsylvania Avenue, N.W.
Washington, D.C. 20037-3202
(202) 293-7060

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